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Original Article

The Effect of Dextran on Colonic Anastomosis During The Early Postoperative Period in Rats

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ABSTRACT

Objective: Anastomotic leakage after colorectal surgery is a serious complication associated with high mortality. Dextran has been reported to reduce blood viscosity and increase microcirculation. This study was conducted to investigate whether postoperative dextran infusion contributes to anastomotic durability.

Methods: A total of 40 Wistar Albino rats were used in the study. There are two experimental groups that received Dextran for 3 and 7 days after colon anastomosis and two control groups that did not receive any treatment. Anastomotic burst pressure score was calculated. Anastomosis healing parameters were evaluated histopathologically.

Results: The median bursting pressure observed with the inflammatory phase experiment group was significantly higher than the inflammatory phase control group (p=0.001). Mucosal re-epithelialization was higher than the control groups in both the inflammatory phase (p=0.005) and the proliferative phase (p=0.007).

Conclusion: Dextran could be considered as a potential treatment for anastomosis protection due to its positive effect on mucosal re-epithelialization and especially its increase in premature burst pressure.

INTRODUCTION

Anastomotic leakage constitutes a critical complication following colorectal surgical interventions. Incidence rates have been documented to range from 6% to 30% post-surgery. Empirical studies indicate that patients exhibiting anastomotic leakage experience considerably elevated mortality rates.[1] Over time, numerous factors have been identified in the etiology of anastomotic leakage, encompassing anastomotic tension, selection of suture materials or staple malfunction, malnutrition, immunosuppression, tissue ischemia, and hypoperfusion, as well as dietary interventions aimed at enhancing microbiome resilience in recent years. Notwithstanding advancements in surgical techniques and antimicrobial prophylaxis, along with an increasing cadre of specialized surgeons operating in high-volume facilities, anastomotic leaks continue to pose a significant concern. Moreover, the recognition that ischemia represents one of the predominant causes of anastomotic leakage has catalyzed focused research in this domain.[1-3]

Dextran is characterized as a complex glucan that elevates the osmotic pressure within the lumen due to its macromolecular structure.[4] It has been extensively recorded that incorporating dextran into infusion solutions after surgery positively influences microcirculation by boosting intravascular osmotic pressure. Dextran is well known for enhancing local blood flow due to its properties that inhibit platelet aggregation and its capacity to lower blood thickness. Dextran 40 modifies erythrocytes by imparting an electronegative charge, which subsequently diminishes erythrocyte clustering. This modification facilitates the transit of erythrocytes through micro vessels.[5] Furthermore, dextran has been reported to significantly augment perfused capillaries.[4,6] Research has demonstrated that a progressive reduction in pancreatic capillary perfusion transpires during episodes of experimental acute pancreatitis, with stabilization of pancreatic microcirculation achievable through dextran infusion.[7] Because of its

unique blood-thinning abilities, Dextran 40 has been used to prevent complications after surgery, including conditions such as deep vein thrombosis and stroke. It has also been used to inhibit early graft patency in microvascular surgery procedures.[8] Low-molecular-weight dextran has been employed by numerous microsurgeons following free tissue transfer due to its advantageous effects on microcirculation.[9] Zhao et al.[10] have indicated that dextran encourages angiogenesis and alleviates ischemic damage in skin tissues, with further implications for increasing collagen deposits and enhancing the tissue healing remodeling stage.

Li et al.[11] determined an increase in the number of peritoneal polymorphonuclear (PMN) cells, especially in the first 6 hours, after intraperitoneal application of RG1192 (a substituted dextran). Furthermore, they reported that RG1192 increased PMN migration without the need for additional cytokines such as IL-8, in other words, it had a chemotactic effect on PMN cells.[11] In another study, RGTA11, a derivative of Dextran, was evaluated in an in vivo wound healing model of colonic anastomosis and demonstrated a significant increase in anastomotic resistance compared to untreated controls.[12]

The mechanical strength of the intestinal wall is provided by the collagen and reticular fibers it contains. Molecules that stimulate the neosynthesis of collagen fibers and prevent their degradation can increase mechanical strength. It has been reported that the use of epidermal growth factor (HB-EGF) and transforming growth factor-β (TGF-β), which are naturally present in the colonic wall, provides beneficial results.[12] Benoit et al.[[13] claimed that RGTA captures and preserves endogenously secreted heparin-binding growth factors such as fibroblast growth factor (FGF), heparin-binding epidermal growth factor (HB-EGF), transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF).[13] As is known, elastase provides the degradation of extracellular matrix proteins (such as elastin and collagen). In the same study, Benoit et al.[13] stated that RGTA11 inhibited plasmin and elastase activity.[13]

Studies indicate that the characteristics of dextran's solubility and rheology are shaped by its molecular weight and branching, where polysaccharides with lower molecular weights show improved solubility in contrast to longer-chain alternatives.[14] Our literature review did not uncover any additional studies addressing the effects of alternative forms of dextran on colonic anastomosis. This investigation sought to elucidate both the macroscopic and microscopic impacts of Dextran 40 (a low-molecular-weight variant of dextran), recognized for its substantial facilitation of microcirculation, on experimental colonic anastomosis.

MATERIALS AND METHODS

This investigation received endorsement from the Animal Experiments Ethics Committee of Trakya University (No: 2022/08, Date: 01/09/2022). The findings of this study are reported in accordance with the ARRIVE (Animal Research: Reporting of in Vivo Experiments) guidelines.

In this research, we utilized a cohort of 40 Wistar Albino female rats. A careful examination of two earlier investigations revealed that there were some notable improvements in healing results, with effect sizes between 0.50 and 0.70.[15,16] Thus, we anticipated a cautious standardized effect size (Cohen's d) of 0.60 for our main outcome metrics. This estimation was derived from the magnitude of differences observed between the treatment and control cohorts in those investigations, relative to the variability within the data. Conducting a two-tailed test at a 5% significance threshold and with 80% statistical power, we established that 10 animals per group (leading to 40 subjects overall) would be sufficient to pinpoint a significant statistical difference.

During the study, the rats resided in see-through polymer containers. The ambient temperature was meticulously maintained at 22±1 degrees celsius. The rats were provided food ad libitum, although they underwent a 12-hour fasting period in preparation for the surgical procedure.

The rats were stratified into four distinct groups. All groups were assessed for the impact of dextran on inflammatory phase metrics, proliferative phase burst pressures, and histological healing scores. The analysis encompassed four groups delineated as follows:

Group I: This cohort served as the inflammatory phase control group (n=10). These specific rats were not administered dextran infusion after the surgical procedure and were euthanized on day three post-op.

Group II: This cohort constituted the inflammatory phase experimental group (n=10). These rats received a daily infusion of 1cc dextran post-operatively and were euthanized on postoperative day 3.

Group III: This cohort functioned as the proliferative phase control group (n=10). Post-surgery, these rats did not get a dextran infusion and were euthanized on the seventh day following the operation.

Group IV: This cohort represented the proliferative phase experimental group (n=10). These rats received a daily infusion of 1cc dextran post-operatively and were euthanized on postoperative day 7.

Rats were subjected to anesthesia through intramuscular administration of 10 mg/kg xylazine and 90 mg/kg ketamine. In the state of general anesthesia, the tails of the rats were subjected to disinfection utilizing a 10% iodine solution. The tail veins were cannulated employing 24 G intravenous cannulas, which were subsequently secured with sutures. The abdominal regions of the rats underwent preoperative disinfection with iodine. A median laparotomy was executed. The cecum was identified, followed by the exposure of the middle colic artery. The anastomosis site was delineated just distal to the middle colic artery. Resection of the colon was performed. The

proximal and distal segments of the colon were anastomosed using 6/0 polypropylene sutures, with eight primary sutures employed for each anastomosis. The abdominal cavity was subsequently closed employing 2/0 silk primary sutures in a single-layer configuration.

The experimental cohorts received an infusion of 1 cc/day of a 10% Dextran 40 solution through a catheter inserted into the tail vein over a duration of 20 minutes. The 10% Dextran 40 infusion was sustained in group II for a period of 3 days and in group IV for 7 days until the time of sacrifice. In contrast, the control group rats were administered a saline infusion of 1 cc/day. Groups I and II were sacrificed on the third day, while groups III and IV were sacrificed on the seventh day by cardiac exsanguination under anesthesia (adhering to the identical anesthetic protocol as the preliminary surgical procedure). Post-sacrifice, the anastomosis were removed with 1 cm margins of both the distal and proximal colon.

Burst pressure assessments were conducted utilizing a transducer. A 20 G cannula was positioned proximally, with both ends secured using 3/0 silk suture, thereby establishing an airtight environment. The anastomosis were inflated underwater with air, and the initial air leaks were recorded as the burst pressure for each anastomosis. Following the acquisition of burst pressure data, tissue samples of the colon containing the anastomosis were immersed in a 10% buffered formaldehyde solution and prepared for subsequent histopathological analysis.

Using hematoxylin-eosin (H&E), slides measuring four to five microns, derived from paraffin blocks, were stained to analyze histopathological changes within the anastomotic region. These slides were examined under a light microscope, and wound healing was evaluated employing the Houdart anastomosis healing parameters[17], as revised by Garcia et al.[18], which included criteria such as re-epithelialization, inflammatory infiltration, necrosis, and granulation tissue formation (Table 1). The samples were scrutinized in the pathology laboratory utilizing an Eclipse Ci-L Nikon light microscope at a magnification of x100. The samples were assessed in a randomized order by a pathologist who was blinded to the group assignments and macroscopic data. Images of the samples were captured utilizing a Nikon DS-L3 camera.

To assess normality, the Shapiro-Wilk test was utilized, defining a significance cutoff of 0.05. In addition to this formal statistical assessment, histograms and Q-Q plots were analyzed to visually corroborate the assumptions regarding distribution. The experimental cohorts underwent a comparative analysis via a one-way ANOVA for datasets conforming to a normal distribution, followed by pairwise evaluations conducted through student's t-test as a post-hoc analysis. In scenarios where the normality condition

Table 1. Parameters of anastomotic healing described by Houdart et al.[17] and revised by Garcia et al.[18]

Anastomotic mucosal re-epithelialization

Grade 0	No epithelization of the anastomotic line
Grade 1	Anastomotic line covered partially by a single layer of cells
Grade 2	Anastomotic line covered completely by a single layer of cells
Grade 3	Complete re-epithelialization with glandular cells

Inflammatory granulomas and granulation tissue formation

	Inflammatory cells	Neovascularization	Fibroblasts	Fibrosis
Grade 1	None	None	None	None
Grade 2	Mild	Mild	Mild	Mild
Grade 3	Moderate	Moderate	Moderate	Moderate
Grade 4	Intense	Intense	Intense	Intense

Muscle layer destruction

	Ischemic necrosis	Muscle Layer Continuity	Inflammatory Infiltration
Grade 1	None	Complete interruption	None
Grade 2	Mild	Muscle Sinechia	Mild
Grade 3	Moderate	Complete restitution	Intense
Grade 4	-	-	-

Anastomotic wound inflammatory infiltration

	Neutrophils	Lymphocytes	Histiocytes	Giant cells
Grade 1	None	None	None	None
Grade 2	Mild	Mild	Mild	Mild
Grade 3	Moderate	Moderate	Moderate	Moderate
Grade 4	Intense	Intense	Intense	Intense

was violated, the Kruskal-Wallis H test was conducted, and notable distinctions were subsequently assessed using the Mann-Whitney U test as the additional analysis. A p-value of less than 0.05 was deemed to be statistically significant. All statistical analyses were conducted utilizing SPSS version 23 (SPSS Inc., Armonk, NY).

RESULTS

Upon conducting an analysis of the bursting pressures, no statistically significant differences were detected between the control group and the experimental group within the proliferative phase (p=0.25); however, the median bursting pressure recorded in the inflammatory phase experimental group was markedly superior to that of the inflammatory phase control group (p=0.001). The median bursting pressures across the various groups are delineated in Table 2.

The data we gathered suggests that the level of mucosal re-epithelialization was considerably more pronounced in the experimental groups throughout both the inflammatory phase (p=0.005) and the proliferative phase (p=0.007) relative to their control groups. The grades of mucosal re-epithelialization are presented in Table 3. Figure 1a illustrates a microscopic image depicting partial re-epithelialization occurring at the anastomosis site of a rat from the inflammatory phase control group. Conversely, Figure 1b displays a microscopic image of complete re-epithelialization in tissue obtained from a rat in the inflammatory phase experimental group.

The analysis revealed no statistically significant difference in neovascularization between the inflammatory phase experimental group and the control group (p=0.056). Although this borderline p-value implies a potential trend towards increased neovascularization within the exper-

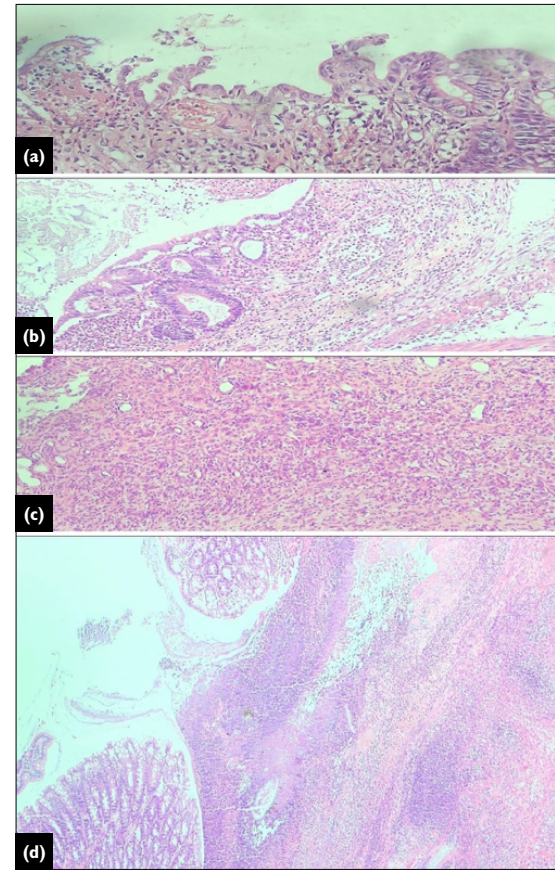

Figure 1. (a) Partial epithelization of anastomosis from a group 1 rat (Haematoxylin – Eosin, x200) **(b)** Complete re-epithelialization with glandular cells from a group 2 rat (Haematoxylin-Eosin, x200) **(c)** Intense fibroblastic activity in Group 4 colon anastomosis (Haematoxylin-Eosin-x100) **(d)** Intense necrosis and inflammation in a Group I anastomosis line (Hematoksilen-Eozin, 40x).

Table 2. Median bursting pressures of the groups

	Group I	Group II	Group III	Group IV	F; p
Anastomotic bursting pressures (mmHg)	45±5.5	66.7±8.6	112±8.7	118.1±13.6	136,64; <0.001
Post-Hoc: p	**<0.001**		0.249		

Table 3. Grades of anastomotic mucosal re-epithelialization of all groups

Anastomotic mucosal re-epithelization, n (%)	**Group I**	**Group II**	**Group III**	**Group IV**	**X^2; p**
Grade 1	5 (50)	0 (0)	1 (10)	0 (0)	
Grade 2	4 (40)	4 (40)	6 (60)	1 (10)	
Grade 3	1 (10)	6 (60)	3 (30)	9 (90)	
Mean±sd	1.6±0.7	2.6±0.52	2.2±0.63	2.9±0.32	
Median (IQR)	1.5 (1-2)	3 (2-3)	2 (2-3)	3 (3-3)	17,32; 0.001
Post-Hoc: p	**0.005**		**0.007**		

Table 4. Inflammatory granuloma and granulation tissue formation data for all groups

Inflammatory cells, n (%)	Group I	Group II	Group III	Group IV	X^2; p
Mild (Grade 2)	3 (30)	1 (10)	0 (0)	1 (10)	
Moderate (Grade 3)	6 (60)	2 (20)	5 (50)	4 (40)	
Intense (Grade 4)	1 (10)	7 (70)	5 (50)	5 (50)	
Mean±sd	2.8±0.63	3.6±0.7	3.5±0.53	3.4±0.7	
Median (IQR)	3 (2-3)	4 (3-4)	3.5 (3-4)	3.5 (3-4)	8,17; 0.043
Post-Hoc: p	**0.015**		0.831		
Neovascularization, n (%)					
Mild (Grade 2)	6 (60)	1 (10)	0 (0)	0 (0)	
Moderate (Grade 3)	3 (30)	8 (80)	4 (40)	5 (50)	
Intense (Grade 4)	1 (10)	1 (10)	6 (60)	5 (50)	
Mean±ss	2.5±0.71	3±0.47	3.6±0.52	3.5±0.53	
Median (IQR)	2 (2-3)	3 (3-3)	4 (3-4)	3.5 (3-4)	15,04; 0.002
Post-Hoc: p	**0.056**		0.661		
Fibroblasts, n (%)					
None (Grade 1)	0 (0)	1 (10)	0 (0)	0 (0)	
Mild (Grade 2)	5 (50)	1 (10)	0 (0)	0 (0)	
Moderate (Grade 3)	5 (50)	5 (50)	4 (40)	0 (0)	
Intense (Grade 4)	0 (0)	3 (30)	6 (60)	10 (100)	
Mean±ss	2.5±0.53	3±0.94	3.6±0.52	4±0	
Median (IQR)	2.5 (2-3)	3 (2.75-4)	4 (3-4)	4 (4-4)	22,29, <0.001
Post-Hoc: p	0.100		**0.029**		
Fibrosis, n (%)					
Mild (Grade 2)	10 (100)	10 (100)	2 (20)	0 (0)	
Moderate (Grade 3)	0 (0)	0 (0)	6 (60)	4 (40)	
Intense (Grade 4)	0 (0)	0 (0)	2 (20)	6 (60)	
Mean±sd	1±0	1±0	2±0,67	2.6±0.52	
Median (IQR)	1 (1-1)	1 (1-1)	2 (1.7-2.2)	3 (2-3)	31,34, <0.001
Post-Hoc: p	1.000		**0.044**		

imental group, such findings must be interpreted with caution owing to the limited sample size, which may have attenuated the statistical power of the study. Given the significant differences observed in burst pressures and mucosal re-epithelialization between these groups, the noted trend in neovascularization may indeed possess clinical significance. Nonetheless, additional studies encompassing larger sample sizes are imperative to ascertain whether the observed increase in neovascularization contributes to the enhanced re-epithelialization and bursting pressures identified in the experimental group.

We also determined significant differences in inflammatory cells, fibroblasts, and fibrosis. The grades of inflammatory cells were markedly elevated in the experimental group during the inflammatory phase compared to the control group of the same phase (p=0.015). The grades of fibroblasts and fibrosis exhibited statistically significant elevations in the experimental group within the proliferative phase as opposed to the control group of that phase (p=0.029, p=0.044, respectively). Figure 1c illustrates pronounced fibroblastic activity within the colon anastomosis of a rat belonging to the proliferative phase experimental group. Data concerning inflammatory granuloma and granulation tissue formation are presented in Table 4.

Regarding inflammation in the muscle layer, no statistically significant variance was observed between the experimental and control groups during the inflammatory phase (p=0.054). In the course of histopathological analysis of the muscular layer, we observed no relevant statistical disparities between the inflammatory and proliferative experimental and control cohorts concerning ischemic necrosis levels (p=0.070, p=0.067, respectively). The data pertaining to muscle layer destruction are depicted in Table 5. Dextran did not exert a substantial impact on the muscle layer; however, it was found to significantly influence the epithelial layer (notably in aspects such as re-epithelialization and the increase of inflammatory cells), suggesting that the observed rise in burst pressure during the inflammatory period may be attributable to these effects.

Neutrophil migration was statistically significantly higher in the inflammatory phase experiment group than in the

Table 5. Muscle layer destruction data of all groups

Inflammatory cells, n (%)	Group I	Group II	Group III	Group IV	X^2; p
Ischemic nekrosis, n (%)					
None (Grade 1)	4 (40)	2 (20)	10 (100)	7 (70)	
Slight (Grade 2)	6 (60)	4 (40)	0 (0)	3 (30)	
Moderate (Grade 3)	0 (0)	4 (40)	0 (0)	0 (0)	
Mean ± sd	1.6±0.52	2.2±0.79	1±0	1.3±0.48	
Median (IQR)	2 (1-2)	2 (1.75-3)	1 (1-1)	1 (1-2)	16,39; 0,001
Post-Hoc: p	0.070		0.067		
Muscle layer continuity, n (%)					
Complete interruption (Grade 1)	0 (0)	1 (10)	0 (0)	0 (0)	
Partial interruption (Grade 2)	9 (90)	8 (80)	1 (10)	2 (20)	
Complete restitution (Grade 3)	1 (10)	1 (10)	9 (90)	8 (80)	
Mean ± sd	2.1±0.32	2±0.47	2.9±0.32	2.8±0.42	
Median (IQR)	2 (2-2)	2 (2-2)	3 (3-3)	3 (2.75-3)	22,09; <0,001
Post-Hoc: p	0.584		0.542		
Inflammation, n (%)					
None (Grade 1)	0 (0)	0 (0)	1 (10)	0 (0)	
Slight (Grade 2)	6 (60)	1 (10)	6 (60)	4 (40)	
Moderate (Grade 3)	2 (20)	5 (50)	3 (30)	6 (60)	
Intense (Grade 4)	2 (20)	4 (40)	0 (0)	0 (0)	
Mean ± sd	2.6±0.84	3.3±0.67	2.2±0.63	2.6±0.52	
Median (IQR)	2 (2-3.25)	3 (3-4)	2 (2-3)	3 (2-3)	10,37; 0,016
Post-Hoc: p	0.054		0.147		

control group (p=0.008). Table 6 presents data on inflammatory cell infiltration. Severe necrosis and inflammation within the anastomosis of a rat from the inflammatory phase control group is depicted in Figure 1d.

DISCUSSION

Surgical resection constitutes the principal therapeutic approach for colorectal malignancies. Surgical intervention grounded in oncological principles is essential for achieving patient recovery; the primary objective is to entirely (en bloc) excise the neoplasm along with the adjacent lymphatic tissues to ensure the presence of clear resection margins.[19] Anastomotic leakage represents the most significant risk associated with post-resection colon anastomosis. In certain instances, diversion ileostomies are executed to safeguard these anastomosis. Nonetheless, the existence of an ostomy, even if transient, adversely impacts the quality of life of patients.[20]

Anastomotic perfusion continues to be the main topic in studies targeting anastomotic strength. Even in the absence of any significant factor, it is stated that the amount of oxygen in the microenvironment decreases significantly in the early stages of wound healing. A statistically significant relationship is defined between decreased perfusion in the anastomosis line and increased colonic anastomosis leakage rates.[3] In an experimental study, it was reported that burst pressure and OH-proline levels significantly increased and TNF-α, IL-6 and IL-10 values were lower in colonic anastomosis treated with hyperbaric oxygen therapy.[21] Consequently, ongoing investigative efforts are concentrated on exploring various materials to enhance the strength and security of colonic anastomosis, thereby eliminating the necessity for ostomy.[22,23]

Dextran 40 is a polysaccharide macromolecule comprised of repetitive glucose subunits, with approximately 50% being eliminated through renal pathways within three hours following intravenous administration. Dextran promotes plasma volume augmentation via its colloidal osmotic effect, which aids in the movement of fluid from the interstitial space into the intravascular space. Data suggests dextran amplifies the electronegativity present in erythrocytes, platelets, and vascular endothelial cell types. Due to this characteristic, it diminishes the aggregation of erythrocytes and other cellular components of the blood. Thus, it reduces the viscosity of the blood. In light of all these factors, it has been asserted that dextran exerts beneficial effects on microcirculation during the postoperative period.[5,24,25]

The reconstruction of autologous free flaps has seen a notable increase in recent years, with evidence suggesting that the principal barrier to the success of free flap procedures is frequently flap thrombosis.[26] Research has demonstrated that vascular occlusion predominantly oc-

Table 6. Data on inflammatory cell infiltration of the anastomosis line

Inflammatory cells, n (%)	Group I	Group II	Group III	Group IV	X^2; p
Neutrophyles, n (%)					
None (Grade 1)	0 (0)	0 (0)	7 (70)	5 (50)	
Mild (Grade 2)	5 (50)	1 (10)	3 (30)	4 (40)	
Moderate (Grade 3)	4 (40)	2 (20)	0 (0)	1 (10)	
Intense (Grade 4)	1 (10)	7 (70)	0 (0)	0 (0)	
Mean±sd	2.6±0.7	3.6±0.7	1.3±0.48	1.6±0.7	
Median (IQR)	2.5 (2-3)	4 (3-4)	1 (1-2)	1.5 (1-2)	26,18; <0,001
Post-Hoc: p	**0.008**		0.313		
Lymphocytes, n (%)					
None (Grade 1)	0 (0)	1 (10)	0 (0)	0 (0)	
Mild (Grade 2)	2 (20)	4 (40)	7 (70)	4 (40)	
Moderate (Grade 3)	7 (70)	4 (40)	2 (20)	5 (50)	
Intense (Skor 4)	1 (10)	1 (10)	1 (10)	1 (10)	
Mean±sd	2.9±0.57	2.5±0.85	2.4±0.7	2.7±0.67	
Median (IQR)	3 (2.75-3)	2.5 (2-3)	2 (2-3)	3 (2-3)	3,69; 0,296
Post-Hoc: p	0.223		0.251		
Hystiocytes, n (%)					
Mild (Grade 2)	7 (70)	6 (60)	2 (20)	0 (0)	
Moderate (Grade 3)	3 (30)	4 (40)	6 (60)	6 (60)	
Intense (Grade 4)	0 (0)	0 (0)	2 (20)	4 (40)	
Mean±sd	1.3±0.48	1.4±0.52	2±0.67	2.4±0.52	
Median (IQR)	1 (1-2)	1 (1-2)	2 (1.7-2.2)	2 (2-3)	16,65; 0,001
Post-Hoc: p	0.648		0,165		
Giant cells, n (%)					
Mild (Grade 2)	10 (100)	8 (80)	3 (30)	3 (30)	
Moderate (Grade 3)	0 (0)	2 (20)	4 (40)	3 (30)	
Intense (Grade 4)	0 (0)	0 (0)	3 (30)	4 (40)	
Mean±sd	1±0	1.2±0.42	2±0.82	2.1±0.88	
Median (IQR)	1 (1-1)	1 (1-1.25)	2 (1-3)	2 (1-3)	15,92; 0,001
Post-Hoc: p	0.146		0.779		

curs in the anastomotic region due to the formation of fibrin. It has been reported that dextran not only mitigates the formation of the fibrin network but also stimulates fibrin degradation.[9] Dextran 40 exerts its antithrombotic properties through its interaction with vascular endothelium, erythrocytes, and platelets, thereby mitigating erythrocyte aggregation and platelet adhesion. It has been reported that platelets coated with dextran are stored more evenly within the thrombus and bind with raw fibrin, simplifying thrombolysis. Similarly, Salemark et al.[27] reported that dextran causes fragile fibrin formation and increases fibrinolysis.[6] A comprehensive meta-analysis has indicated that the administration of dextran-40 may diminish the likelihood of partial flap failure by approximately 46%, albeit it is concomitantly associated with the potential for grave complications, including atelectasis, pulmonary edema, and anaphylaxis.[28] Despite ongoing deliberations regarding its infrequent yet significant complications and clinical advantages in contemporary discourse, dextran has remained a preferred agent among reconstructive surgeons for numerous years, serving as a protective substance in free tissue transfer, post-digital transplantation, and post-anastomotic revision.[29]

To ascertain a reliable colonic anastomosis, it is imperative to minimize tension while sustaining optimal perfusion. While a variety of surgical approaches have been proposed to reduce anastomotic tension, studies have also focused on anastomotic perfusion.[30] Our hypothesis was that postoperative dextran infusion could improve microcirculation in the colon anastomosis and thus increase perfusion along the anastomotic area.

Burst pressure has long been used as a measure of anastomotic strength. Values for burst pressure experience a rapid increase within the initial seven days following anastomosis; however, subsequent to this period, a plateau is observed.[31] In our investigation, we assessed the burst pressures of the cohorts receiving dextran for durations

of 3 and 7 days in comparison to those devoid of dextran. Upon analysis of the groups concerning burst pressures, no significant differences were discerned between the proliferative phase cohorts regardless of dextran administration. However, inflammatory phase experimental group anastomosis exhibited higher burst pressure than inflammatory phase control group anastomosis ($p<0.001$); this finding implies that dextran infusion may have bolstered anastomotic mechanical strength during the inflammatory phase of healing. Histological indicators also supported this situation. In our research, we noted a higher infiltration of inflammatory cells in the inflammation phase experimental group relative to the inflammation phase control group.

The healing process of intestinal anastomosis adheres to the identical stages observed in skin wound healing: inflammation, proliferation, and remodeling. In the inflammatory healing phase, a cytokine-laden setting arises at the point of injury. This phenomenon augments the permeability of adjacent small vessels, thereby facilitating the migration of inflammatory cells to the locus of injury. After platelets have aggregated, neutrophils respond first, and macrophages then arrive at the site of the damage.[32] Similarly, in our study, the notable increase in the quantity of inflammatory cells observed in the experimental group on the third day in comparison to the control group may serve as an indicator of the beneficial influence of dextran during the inflammatory phase.

Houdart et al.[33] established that neovascularization can be detected angiographically as early as three days post-anastomosis, with a peak occurrence observed on the seventh day. The investigation did not uncover a statistically significant variation in neovascularization between the dextran-treated cohort and the control cohort on either the third or seventh day, yet the p-value of 0.056 from the three-day dextran-treated group versus the control group is of interest. This p-value may be attributed to the constraints imposed by a limited sample size. The infusion of dextran may have resulted in elevated burst pressures by ameliorating the perfusion deficit engendered by insufficient neovascularization during the initial three days. Gelin et al.[34] noted that dextran exerts a beneficial effect on aberrant capillary permeability, but does not influence normal capillary permeability. The observation that dextran does not significantly enhance neovascularization and burst pressures during the proliferative phase may be elucidated by the attenuation of its efficacy on anastomosis due to the amelioration of capillary permeability throughout this phase.

Dextran minimizes the congregation of red blood cells and platelets while concurrently softening erythrocyte rigidity, thereby easing their journey through fine blood vessels. As a result, a notable enhancement in microcirculation is observed.[5] The study conducted by Alam et al.[35] indicated that resuscitating with dextran 40 in a model of experimental hemorrhagic shock activated neutrophils. In another study, it was reported that after intraperitoneal injection of RG1192, a substituted dextran, there was a five-fold increase in the peritoneal polymorphonuclear cell count at 6 hours and a three-fold increase at 24 hours compared to the control groups.[11] Similarly, in our study, we also found statistically significant higher neutrophil counts at the anastomosis site during the inflammatory phase in the dextran-treated group.

To assess anastomotic healing, the grading system initially delineated by Houdart and subsequently updated by Garcia remains pertinent.[17,18] These investigations have provided a comprehensive classification of the histopathological dimensions pertinent to anastomotic healing. We employed this grading system to appraise anastomotic healing in our investigation (Table 1). In our analysis, we found that the dextran-treated groups displayed higher rates of re-epithelialization on both the third and seventh days when set against the control groups. This observation may be ascribed to the capacity of dextran to enhance tissue perfusion.[25,36,37]

During the inflammatory phase, fibroblasts are recruited to the cut edge of the intestine as a consequence of the release of chemotactic factors, such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and fibroblast growth factor (FGF) by macrophages. Fibroblasts commence to appear in the latter stages of the inflammatory phase, subsequently becoming the predominant cell type within the wound bed during the initial proliferative phase. In the proliferative phase, the count of inflammatory cells, particularly neutrophils and macrophages, that were once more prevalent, begins to lessen. During the proliferative phase associated with anastomotic healing, the chief duty of fibroblasts involves laying collagen at the wound's base. Additionally, they facilitate the transition of the transient fibrin clot into granulation tissue.[32] Sufian and colleagues clarified that administering fibroblasts within the wall positively impacts the integrity of anastomosis.[38] In our study, no significant disparity was observed between the fibroblast and fibrosis metrics within the control and treatment cohorts during the inflammation phase; however, augmented fibroblastic activity and fibrosis were noted in the dextran group on the seventh day when juxtaposed with the control cohort.

In conclusion, both dextran-treated cohorts manifested elevated levels of re-epithelialization. We found that neutrophils in the inflammatory phase and fibroblasts and fibrosis in the proliferative phase increased significantly in the groups treated with dextran. We also determine that anastomotic bursting pressure increased in the inflammatory phase in rats that received dextran infusion. The limitation of this study is that the sample size is restricted due to its experimental nature. Our study is also limited in terms of determining the optimal dose for dextran, as it did not include a dose other than 1 mg per day. However, it was possible to evaluate the effects of dextran on different stages of anastomotic healing (inflammatory and proliferative). Future studies can be conducted with different doses to evaluate the optimal effects of dextran on anastomosis. Additionally, this study may guide future

research focusing on dextran-based products that can be applied directly to anastomosis.

Ethics Committee Approval

The study was approved by the Animal Experiments Ethics Committee of Trakya University Ethics Committee (Date: 01.09.2022, Decision No: 2022/08).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: Z.T., O.A.Ö.; Design: Z.T., O.A.Ö., E.G.E.; Supervision: Z.T.; Funding: Z.T.; Materials: Z.T., O.A.Ö., E.G.E.; Data collection &/or processing: Z.T., O.A.Ö., E.G.E.; Analysis and/or interpretation: Z.T., O.A.Ö.; Literature search: Z.T., O.A.Ö., E.G.E.; Writing: Z.T., O.A.Ö.; Critical review: Z.T.

Conflict of Interest

None declared.

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Sıçanlarda Erken Postoperatif Dönemde Kolon Anastomozları

Amaç: Kolorektal cerrahiden sonra anastomoz sızıntısı yüksek mortalite ile ilişkili ciddi bir komplikasyondur. Dekstranın kan viskozitesini azalttığı ve mikrosirkülasyonu artırdığı bildirilmiştir. Bu çalışma, postoperatif dekstran infüzyonunun anastomoz dayanıklılığına katkıda bulunup bulunmadığını araştırmak için yürütülmüştür.

Gereç ve Yöntem: Çalışmada toplam 40 Wistar Albino sıçanı kullanılmıştır. Kolon anastomozundan sonra 3 ve 7 gün boyunca Dekstran alan iki deney grubu ve herhangi bir tedavi almayan iki kontrol grubu bulunmaktadır. Anastomoz patlama basıncı skoru hesaplanmıştır. Anastomoz iyileşme parametreleri histopatolojik olarak değerlendirilmiştir.

Bulgular: İnflamatuvar faz deney grubunda gözlenen medyan patlama basıncı, inflamatuvar faz kontrol grubundan anlamlı derecede yüksekti ($p=0.001$). Mukozal re-epitelizasyon, hem inflamatuvar fazda ($p=0.005$) hem de proliferatif fazda ($p=0.007$) kontrol gruplarından daha yüksekti.

Sonuç: Dekstran, mukozal re-epitelizasyon üzerindeki olumlu etkisi ve özellikle erken patlama basıncını artırması nedeniyle anastomoz koruması için potansiyel bir tedavi olarak düşünülebilir.

Anahtar Sözcükler: Anastomoz; anastomoz sızıntısı; dekstran; kolon; patlama basıncı.